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Abstract: Background Huntington's disease (HD) is a rare, progressive neurodegenerative disease. Currently, there is no cure for the disease, but treatment may alleviate HD symptoms. In recent years, several exercise training interventions have been conducted in HD patients. In the current article, we review previous studies investigating targeted exercise training interventions in HD patients. Methods We performed a literature search using the PubMed, Scopus, Web of Science, and Google Scholar databases on exercise training interventions in HD patients. Six publications fulfilled the criteria and were included in the review. Results Exercise training resulted in beneficial effects on cardiovascular and mitochondrial function. Training effects on cognition, motor function, and body composition were less congruent, but a positive effect seems likely. Health-related quality of life during the training interventions was stable. Most studies reported no related adverse events in response to training. Discussion Exercise training seems to be safe and feasible in HD patients. However, current knowledge is mainly based on short, small-scale studies and it cannot be transferred to all HD patients. Therefore, longer-term interventions with larger HD patient cohorts are necessary to draw firm conclusions about the potentially positive effects of exercise training in HD patients.

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Reviews

Exercise in Huntington's Disease: Current State and Clinical Significance

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Abstract

Background: Huntington's disease (HD) is a rare, progressive neurodegenerative disease. Currently, there is no cure for the disease, but treatment may alleviate HD symptoms. In recent years, several exercise training interventions have been conducted in HD patients. In the current article, we review previous studies investigating targeted exercise training interventions in HD patients.

Methods: We performed a literature search using the PubMed, Scopus, Web of Science, and Google Scholar databases on exercise training interventions in HD patients. Six publications fulfilled the criteria and were included in the review.

Results: Exercise training resulted in beneficial effects on cardiovascular and mitochondrial function. Training effects on cognition, motor function, and body composition were less congruent, but a positive effect seems likely. Health-related quality of life during the training interventions was stable. Most studies reported no related adverse events in response to training.

Discussion: Exercise training seems to be safe and feasible in HD patients. However, current knowledge is mainly based on short, small-scale studies and it cannot be transferred to all HD patients. Therefore, longer-term interventions with larger HD patient cohorts are necessary to draw firm conclusions about the potentially positive effects of exercise training in HD patients.

Keywords: Resistance training, endurance training, cardiovascular function, motor function, cognition, body composition

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Background

Huntington's disease (HD) is a rare, inherited neurodegenerative disorder. Clinical symptoms of HD encompass motor and non-motor domains. Motor, cognitive, psychological, and behavioral functions may be progressively impaired before the diagnosis of HD is made,^{1,2} and result in limitations of daily activities.³ In later disease stages, patients are dependent on caregivers. To date, there is still no causative treatment for HD. Most treatment approaches intend to alleviate HD symptoms, but none of them has a long-term disease-modifying effect.^{4,5} Accordingly, the aim of symptomatic treatments is to maintain quality of life and independency for as long as possible.

Multiple approaches were introduced to cope with the diversity of HD symptoms, encompassing physical, cognitive, and drug therapy. Physical therapy was integrated in the treatment process decades ago

in order to attenuate impairments in motor function,^{6,7} and focused on task-specific exercises to imitate and improve activities of daily living. Studies with physical therapy interventions showed an improvement in specific tasks or at least an attenuation of the natural disease progress for these tasks.^{8–16}

Based on the close relationship between some physical therapy exercises and resistance or endurance exercise, interest was aroused in whether the last two training modalities might have an effect in HD patients. However, several years ago, the potential benefits of exercise interventions were clouded by suspected disadvantages. On the one hand, it was known that a passive lifestyle might lead to an earlier age at symptom onset in HD patients,¹⁷ and that exercise exerts a positive effect in other neurodegenerative diseases, e.g. amyotrophic lateral sclerosis and Parkinson disease.^{18,19} On the other hand, a case study

postulated a relationship between excessive endurance training and acute myopathy with rhabdomyolysis in a semi-professional marathon runner with premanifest HD.²⁰ In conjunction with skeletal muscle mitochondrial impairments in HD patients,^{21–24} a negative effect of excessive training on skeletal muscle energy metabolism was suspected. Nonetheless, based on the promising results of the first studies and an overwhelming proportion of studies showing a positive effect of exercise in the HD mouse model (for a review see Mo et al.²⁵), several studies investigated the effects of structured exercise training in HD patients within the last 5 years.

In this article, we review and summarize the findings of previous studies assessing the effects of targeted exercise training interventions in HD patients. This review refers only to studies applying structured endurance and/or resistance training programs with quantitative outcome data in human patients. Readers interested in the effects of physical therapy and multidisciplinary rehabilitation interventions in HD are referred to a recent review by Fritz et al.²⁶

Methods

We searched the PubMed, Scopus, Web of Science, and Google Scholar databases using variant names of the disease, i.e. “Huntington disease” or “Huntington’s disease”, in combination with exercise intervention-related terms, i.e. “exercise”, “training”, “endurance”, “resistance training”, “resistance exercise”, “strength training”, and “strength exercise”. In addition, the reference lists of included articles were screened for further candidate publications. The search was restricted to articles in the English language involving human HD patients. In the current review, we included scientific literature on structured exercise intervention programs incorporating targeted endurance and/or resistance training. Exercise training is defined as a structured, purposefully planned activity that can be progressed by means of volume and/or intensity changes. Quantitative data on the effects of training were necessary for inclusion in the review. We conducted the search in October 2018 and all publications up to the date of the search were screened.

The search identified 1,407 candidate publications (Fig. 1). After removal of duplicates ($n=341$), 1,066 candidate publications remained. Afterwards, we screened the abstracts of all articles to check if they fell in to the scope of this review. Based on the available abstracts, 1,003 articles were excluded because of lack of relevance. The full texts of the remaining 63 articles were screened for eligibility. Fifty-seven full-text articles were excluded for the following reasons: acute or cross-sectional study ($n=30$), reviews ($n=9$), task-specific training ($n=9$), discontinuous training protocol ($n=3$), insufficient description of exercise protocol ($n=2$), no quantitative data ($n=1$), and case studies ($n=3$). Finally, six publications were included in the review, two of which were from our own research group (Table 1).

Results

Study characteristics

The training group size in the included studies consisted of nine to 16 HD patients who completed the interventions. The average age of

the participants was in all studies between 53 and 55 years with reported standard deviation (SD) between 7 and 13 years. In two publications, only male HD patients were included in the analyses. In three studies, the proportion of male and female HD patients was similar, while in a further study, sex of the patients was not reported. The duration of the training interventions ranged between 8 and 26 weeks (Table 1). Frequency of training could be divided into two categories (Table 1). On the one hand, patients were supervised during every training session and had three training sessions per week (four studies).^{28,30–32} On the other hand, patients had only one supervised training session per week. In addition, patients were advised to exercise at home twice a week (two studies).^{27,29} Training protocols differed largely between the studies. Most of the training protocols (four studies)^{27–30} included endurance and resistance exercises, while in our two publications,^{31,32} the results of an exclusive endurance training intervention were presented. In the last two publications, endurance training consisted of periods of constant-load moderate-intensity and high-intensity interval protocols, as well as the combination of these modalities. In the two studies with supervised and unsupervised training sessions, the supervised sessions consisted of constant-load low-/moderate-intensity endurance training for 10–30 minutes and whole-body resistance training, mainly targeting major muscle groups.^{27,29} Home-based training consisted of walking at a low exercise intensity. In a further study, patients exercised three times a week at home with an exercise DVD, including a whole-body resistance training program.²⁸ In addition, they were advised to go for a gradual progressive walk at light subjective exercise intensity. Over all the studies, training intensity for the supervised constant-load endurance exercise sessions was between 55% and 85% of (age-predicted) maximum heart rate for the constant-load session. In the high-intensity training protocol, the target heart rate was 90–95% of predetermined peak heart rate. Training intensity for the resistance training interventions was 60–70% of one-repetition maximum,²⁷ not reported,²⁸ or was defined by sets and repetitions,^{29,30} with the remark that patients were encouraged to exceed these numbers to ensure training progression (Table 1).

Adverse events

Information about adverse events in response to the training intervention was reported in all included publications (Table 2). Five studies reported no related adverse events in the intervention group.^{27–29,31,32} Quinn et al.³⁰ reported two adverse events in the intervention group. Namely, recurrence of back pain ($n=1$) and Wolf-Parkinson-White syndrome ($n=1$) were observed, which resulted in withdrawal of the patients. In the same study, two serious adverse events were reported in the control group (i.e. attempted suicide possibly related to the study and a suicide unlikely to be related to the study).

Effects on motor function

Four studies reported the Unified Huntington’s Disease Rating Scale (UHDRS) motor score or a modified UHDRS motor score before and after the training intervention (Table 2).^{27,28,30,31} Two studies reported lower motor scores after the intervention (-2.3 in

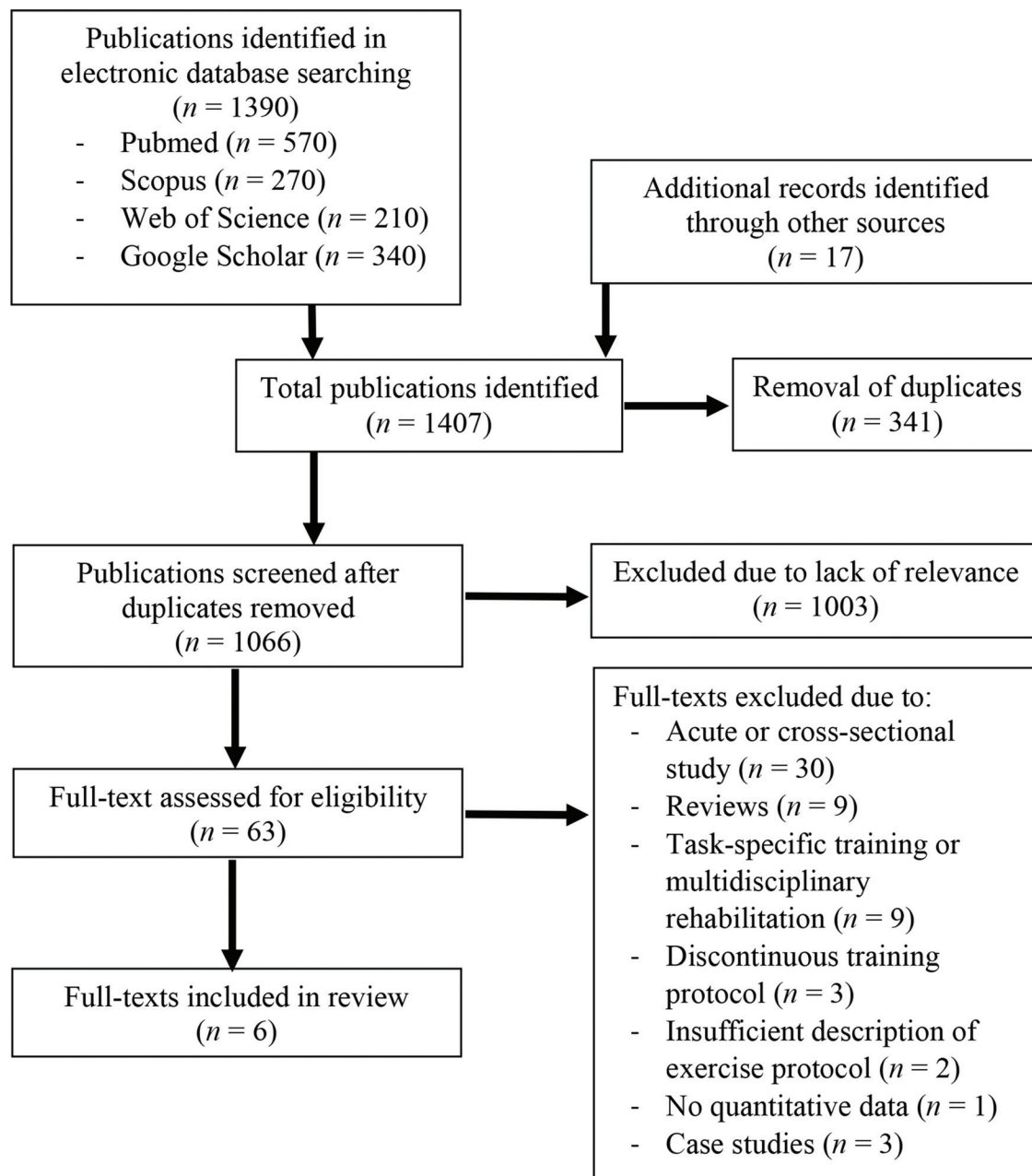


Figure 1. Flow Chart of the Study Selection Process.

8 weeks and -2 in 12 weeks), with significant group \times time interactions, compared with alterations in a HD control group.^{28,30} Two studies reported statistically not altered values ($+3.9$ in 12 weeks and $+0.8$ in 26 weeks).^{27,31} In all four studies, information on the natural disease progression of motor scores was also included. In one of our publications, natural disease progression of the UHDRS motor score was assessed in the 26 weeks before onset of the training intervention in the same HD patients.³¹ The UHDRS motor score increased significantly in this first inactive period by an average of 7.4 points, while the increase was almost completely attenuated ($+0.8$) during the

training intervention. In the further three studies, data of a HD control group were reported. In all these studies, motor scores remained within ± 3 points during the observation period.^{27,28,30}

Effects on mobility

During the training intervention, self-selected gait speed was stable in one study²⁷ and improved in another study.²⁸ Performance during the 3-minute (one study)³⁰ and 6-minute (one study)²⁷ walk tests were not altered in response to the training interventions. Repeated chair stand test performance was not altered in two studies,^{27,30} but the

Table 1. Characteristics of the Endurance and Resistance Training Interventions in Huntington's Disease Patients

	Duration	Frequency	ET			RT		
			ET Intervention	ET Duration	ET Intensity	RT Intervention	RT Duration	RT Intensity
Busse et al. ²⁷	12 weeks	1 × /week (c) 2 × /week (h)	Cycling CLT (c) walking (h)	20–30 min (c) 10–30 min (h)	55–75% of predicted HR _{max} (c) Borg value: 3–4 (h)	Leg press, leg extension, lat pulldown, hamstring curl, calf raises	40 min (c)	2 × 8–12 repetitions 60– 70% 1RM, progressive
Khalil et al. ²⁸	8 weeks	3 × /week	Gradual progressive walk program	30 min	Light subjective exercise intensity	Circuit resistance training and strengthening exercises	n.r.	Gradually increase number of repetitions and increase difficulty of exercises
Dawes et al. ²⁹	12 weeks	1 × /week (c) 2 × /week (h)	Cycling CLT (c) walking (h)	20–30 min (c) 10–30 min (h)	55–75% of predicted HR _{max} (c) Quickly but still able to talk (h)	Leg press, leg extension, lat pulldown, hamstring curl, calf raises	n.r.	2 × 8–12 repetitions, progressive
Quinn et al. ³⁰	12 weeks	3 × /week	Cycling CLT	up to 30 min	65–85% of age predicted HR _{max}	Chair stand, seated wood chop, plank by wall, chair lunge	10–15 min	2 × 10–15 repetitions, progressive
Frese et al. ³¹	26 weeks	3 × /week	Cycling CLT and/or HIIT	30–50 min	65% $\dot{V}O_{2peak}$ (CLT) 90–95% HR _{peak} / 70–85% $\dot{V}O_{2peak}$ (HIIT)	–	–	–
Mueller et al. ³²	26 weeks	3 × /week	Cycling CLT and/or HIIT	30–50 min	65% $\dot{V}O_{2peak}$ (CLT) 90–95% HR _{peak} / 70–85% $\dot{V}O_{2peak}$ (HIIT)	–	–	–

Abbreviations: 1RM, One-repetition Maximum; (c), Supervised Session at Clinic; (h), Session at Home; CLT, Constant-load Training; ET, Endurance Training; HIIT, High-intensity Interval Training; HR, Heart Rate; min, Minutes; n.r., Not Reported; RT, Resistance Training.

Table 2. Outcomes of Training Intervention Studies in Huntington's Disease Patients

AE	Cognition	Motor Function	Quality of Life	Cardiovascular Function	Body Composition	Further Variables
Busse et al. ²⁷	No related AE → UHDRS cognitive score	→ UHDRS motor score, self-selected + fast gait speed, 6-min walk test, CSTS, Romberg No falls	↑ SF-36 mental component score → SF-36 other	→ HR at submaximal power	–	–
Khalil et al. ²⁸	No related AE	↑ UHDRS motor score, gait speed, BBS, CSTS, PPT No falls	→ SF-36	–	–	–
Daves et al. ²⁹	No AE	–	–	→ BP + HR at submaximal power	↑ total body mass	–
Quinn et al. ³⁰	2 AE intervention, 2 SAE control	→ category + verbal fluency, Stroop tests, TMT	→ EQ-5D-3L	↑ predicted $\dot{V}O_{2peak}$	→ total body mass	–
Frese et al. ³¹	No AE	→ DRS-2, HVL-T-R, verbal category fluency, Stroop tests, TMT, SDMT	→ UHDRS motor score	↑ $\dot{V}O_{2peak}$, P_{peak} , T_{lim}	→ total lean mass ↓ fat mass	–
Mueller et al. ³²	No AE	–	–	–	–	↑ CS activity, complex III + V activity, SCCR ↓ relative complex I + II activity ↑ PETF, L^- , PCI, P, ETS, COX

Abbreviations: →, Stable/Not Significantly Altered; ↑, Improvement; ↓, Reduction; AE, Adverse Event; BBS, Berg Balance Scale; BP, Blood Pressure; COX, Respiratory Capacity of Complex IV; CS, Citrate Synthase; CSTS, Chair Stand Test; DRS-2, Mattis Dementia Rating Scale; EQ-5D-3L, Three-level Version of the EuroQol Five-dimensional Questionnaire; ET, Endurance Training; ETS, Electron Transport System Capacity; HR, Heart Rate; HVL-T-R, Hopkins Verbal Learning Test-Revised; L^- , lactate; P, oxidative phosphorylation capacity; PCI, Respiratory Capacity of Complex I; PETF, Fatty Acid Oxidative Capacity; P_{peak} , Peak Cycling Power; PPT, Physical Performance Test; SAE, Serious Adverse Event; SCCR, Succinate Cytochrome c Reductase; SDMT, Symbol Digit Modalities; SF-36, Short Form (36) Health Survey; T_{lim} , Cycling Time-to-Exhaustion; TMT, Trail Making Trials; UHDRS, Unified Huntington's Disease Rating Scale; $\dot{V}O_{2peak}$, Peak Oxygen Uptake.

30-second chair stand test performance was improved in another study.²⁸ One study reported an improved result in the physical performance test after the intervention.²⁸

Effects on balance/postural stability and falls

Balance assessments indicated an improved (Berg Balance Scale)²⁸ or not altered (Romberg test)²⁷ outcome. Two studies reported that no falls occurred in the intervention group during the study period,^{27,28} while a slightly lower number of falls was reported in the intervention group than in the control group in a third study.³⁰

Effects on cognition

Three studies assessed cognitive variables before and after the training intervention (Table 2).^{27,30,31} In most of the assessed cognitive variables, stable values or no significant alterations could be detected during the training interventions. In these studies, the UHDRS cognitive score and/or the Hopkins Verbal Learning Test-Revised (HVLT-R), verbal and category fluency, Stroop/color word interference test, trail making trials, and symbol digit modalities tests were conducted.

Effects on cardiovascular function

In one of our publications with exclusive endurance training, improvements in $\dot{V}O_{2peak}$, peak power, and time-to-exhaustion at 85% of peak power were observed (Table 2).³¹ Another study reported an increase in predicted $\dot{V}O_{2max}$ following resistance and endurance training.³⁰ In two further studies, heart rate at a submaximal cycling power was not altered during the training intervention.^{27,29} One of these later studies also reported stable blood pressures at a submaximal cycling power.²⁹

Effects on body composition

In one study, body composition analysis was performed by dual-energy X-ray absorptiometry (Table 2).³¹ In this study, there were no alterations in total body mass and lean mass, while fat mass was significantly reduced after a 6-month endurance training intervention.³¹ In two further studies, total body mass was reported. In one study, patients exhibited a significant increase in total body mass,²⁹ and in the other study, body mass remained constant in the intervention group.³⁰

Effects on mitochondrial function

In one of our own publications, absolute values for citrate synthase, complex III, complex V, and succinate cytochrome c reductase activities, measured spectrophotometrically, increased significantly during the intervention period (Table 2).³² In contrast, relative complex I and II activities decreased similarly in HD patients and healthy control participants. Mitochondrial respiration measurements in a subgroup of patients revealed significantly improved mass-specific fatty acid oxidative capacity, respiratory capacity of complex I, oxidative phosphorylation capacity, electron transport system capacity, and respiratory capacity of complex IV in response to the training intervention, while mitochondria-specific respiratory capacities remained constant.

Effects on quality of life measures

In three studies, quality of life was assessed by the Short Form (36) Health Survey (SF-36) or by the three-level version of the EuroQol five-dimensional questionnaire (EQ-5D-3L; Table 2).^{27,28,30} Quality of life was stable during the training interventions in two studies.^{28,30} In one study, the mental component of the SF-36 was improved after the training intervention, while the other components of the SF-36 remained stable.²⁷ The control groups in these studies did not exhibit significant worsening of quality of life measures.

Discussion

In our current review, we included six studies on the effects of structured and targeted exercise training in HD patients. A multitude of outcome variables were investigated in these studies, including variables on safety, motor function, cognition, cardiovascular and mitochondrial function, body composition, and quality of life. Most of the studies revealed improved or stable values for the investigated variables during the intervention period.

Safety of the intervention is a main priority when implementing a new treatment approach in HD patients. All the reviewed articles included information about adverse events during the training intervention. Except from one study,³⁰ no training-related adverse events were reported. Since the reported concomitant conditions were aggravated during the training interventions, both patients were withdrawn from the study.³⁰ Based on the data available, endurance and resistance training seem to be safe in HD patients. Nonetheless, in HD, any accelerated worsening of any measured variable might also represent a safety issue. The comparisons between the alterations of measured variables during the training interventions and worsening during natural disease progression will be discussed within every subsequent topic.

Skeletal muscle atrophy is supposed to be a primary health risk in HD patients.³³ However, several cross-sectional studies in early- and mid-stage HD patients could not detect significant differences in fat-free mass or lean mass in comparison to age-matched healthy controls.^{31,34–36} These studies highlighted that observed alterations in muscle mass in HD patients rely on a multitude of factors, e.g. physical activity and nutrition. In theory, the increased skeletal muscle turnover in response to physical activity and training might represent a risk for HD patients prone to muscle atrophy. In contrast, an increased skeletal muscle mass in response to resistance training would represent a promising option to alleviate this condition. Four of the included studies did incorporate resistance exercises in the training program.^{27–30} Unfortunately, none of these studies determined body composition. Two studies reported total body mass before and after the training intervention. Total body mass was not altered in one study³⁰ and was significantly increased (~ 3 kg) in the other study.²⁹ However, information about the composition of these body mass alterations is lacking. In a further study on multidisciplinary rehabilitation in HD patients, incorporating resistance training in the exercise intervention, a significant increase in whole-body fat-free mass was reported.³⁷ Based on the available results, exercise training seems not to accelerate skeletal muscle atrophy in HD patients. On the contrary, resistance training

might even have the potential to increase body mass in early- and mid-stage HD patients. Further investigations of structured resistance training in HD patients with exact body composition measurements are desirable. In addition, we would like to point out that every training intervention should be accompanied by nutrition counseling to prevent a loss of skeletal muscle mass due to inadequate energy and protein intake.

In addition to skeletal muscle atrophy, skeletal muscle mitochondrial impairments are another constraint of peripheral tissue in HD patients.^{21–24,38} The results of one of our own publications indicated that mitochondrial content was increased in response to endurance training, while mitochondrial quality remained stable.³² This result emphasized that mitochondrial biogenesis is physiologically possible in early- and mid-stage HD patients. Besides the increased mitochondrial content, we also observed a rise in the overall capillary-to-fiber ratio during endurance training. The baseline values and the increase in capillarization were similar to the one measured in healthy control participants, indicating that capillarization and angiogenesis are well maintained in early- and mid-stage HD patients compared with that in healthy controls.

Our aforementioned results implicate that oxygen exchange between blood and muscle fibers and oxygen utilization of skeletal muscle fibers are improved after endurance training. This represents one explanation for the reported improvement in (predicted) $\dot{V}O_{2peak}$ in two studies. Otherwise, no study has measured cardiac output before and after the training intervention, whereby information on cardiac adaptations remain unknown. Two studies that measured heart rate at a submaximal cycling power question the occurrence of ventricular hypertrophy in their patients.^{27,29} In both studies, the heart rate at a similar cycling power was not altered before and after the training intervention. Provided that significant ventricular hypertrophy was present, a reduction in heart rate at an identical cycling intensity would be expected. However, in both studies, no further cardiovascular variables were reported, whereby it remains incomprehensible whether the specific training protocols resulted in any cardiovascular adaptation. Epidemiological studies on the immediate causes of death in HD indicated that cardiovascular diseases are the second leading cause behind pneumonia.^{39–41} Since it is well known that physical activity and cardiovascular fitness lead to a reduction in cardiovascular mortality in the general public,^{42,43} a similar effect might be present in HD patients. However, two recent reviews have summarized incidences of cardiac (autonomic) dysfunctions in HD patients and highlight a potential cardiac risk.^{44,45} Hence, further data on cardiovascular adaptations following exercise training interventions in HD patients are required to elucidate health-related cardiovascular benefits and to examine the effects on potential cardiac dysfunctions.

In most included studies, exercise training had a positive effect on motor function. A quantification of the positive effect on the UHDRS motor score is difficult due to the variability in the progression of UHDRS motor scores in the control groups. Data in three studies provide an inconsistent outcome regarding the natural disease progression of the UHDRS motor score.^{27,28,30} In one of our publications,

the natural disease progression of the UHDRS motor score was markedly attenuated during the intervention phase.³¹ The value attained for the natural disease progression in our own study was markedly higher than the reported longitudinal change in the UHDRS motor score in larger cohort studies (3.2 ± 8.4 in 6 months⁴⁶ or 4.7 per year⁴⁷). The explanation for this latter comparison might be based on the high interindividual variation in UHDRS motor score progression.^{48,49} For example, due to the low sample sizes in all training intervention studies, no allocation of HD patients according to motor subtypes was feasible. Further assessed motor functional variables, namely gait speed, walk tests, and chair stand tests, exhibited stable values during the training interventions.^{27,30} Only in the study by Khalil et al.²⁸ were significant improvements in the Berg Balance Scale, gait speed, 30-second chair sit to stand test, and physical performance test reported in relation to the HD control group. However, for all these variables the significant improvement depicted mainly a catch-up effect to the better baseline values of the control group. Based on current results of exercise training on motor function, natural disease progression of HD patients might be attenuated by the interventions. Whether this attenuation has a functional benefit on activities of daily living remains unknown. To gain further insights into the functional benefit of training on activities of daily living, prolonged interventions are necessary.

Over all studies, most assessed cognitive variables were not significantly altered during the training interventions. In comparison to the natural disease progression for cognitive variables,^{50–53} it remains ambiguous whether the training interventions highlight a stabilization of values or slowing of the natural disease progression. In several large-scale investigations, significant decreases in some, but not all, cognitive test variables were detected after 12 months of observation, while these alterations were consolidated after 24 and/or 36 months.^{50–52} Since the duration of training interventions in the included studies ranged from 8 to 26 weeks, the length of the observation period, but also the relatively small size of intervention cohorts, might have been insufficient to detect significant alterations in cognitive variables. This argument is supported by the non-altered cognitive variables in our 6-month natural disease observation period,³¹ and by the statistically not significant alterations in the HD control groups in other studies.^{27,30} Significant improvements in some cognitive variables were previously reported in studies on multidisciplinary rehabilitation in HD patients.^{37,54} In one of these studies, significant improvements were positively correlated with the change in gray matter volume in the dorsolateral prefrontal cortex.⁵⁴ This latter result might even point to preserved neuroplasticity in HD patients.

Self-reported quality of life seems not to be influenced by exercise training in HD patients, nor was it changed during the observation phases in control groups. However, the results might be explained by the low sensitivity of the questionnaires. While it is well known that quality of life is inversely associated with increasing stages of the disease^{55–58} and increased symptoms are associated with lower quality of life,^{59,60} less is known about the magnitude of longitudinal changes in quality of life.⁶¹ Indeed, there is currently no health-related

quality of live measure recommended to measure change of severity over time.⁶²

Limitations of previous studies and future perspectives

The included studies have several limitations that might compromise the outcome of these studies and, thereby, affect the interpretation in this review. First, training intensity for endurance exercise programs was sometimes very low. While training intensity in the supervised training session was moderate to high, home-based endurance training consisted mainly of walking exercise. Since supervised sessions were only conducted once per week and home-based walking twice per week, the overall intensity of these endurance training protocols might not have been sufficient to achieve a significant training effect. Furthermore, patients in the mid- or late-stage of the disease might not be able to achieve a sufficiently high training stimulus due to motor and cognitive impairment. Therefore, exercise training might be a valid strategy to modulate disease symptoms only during early- to mid-stages of HD. Second, in most studies incorporating resistance exercise, important information about resistance exercise determinants⁶³ is missing. These deficits complicate the interpretation of resistance training effects. We recommend that all relevant exercise determinants are reported for resistance and endurance training programs in future studies. Furthermore, it remains to be elucidated which training volume, intensity, and modality best modulates disease symptoms. Third, only one study included exact measurements of body composition. Based on the potential risk that a training intervention might accelerate skeletal muscle atrophy, training intervention studies should incorporate exact body composition measurements and nutrition counseling. Fourth, individual progress adumbrates that adaptation to the training stimulus underlies large interindividual variability. Therefore, studies with larger cohorts might shed more light on the individual alterations in variables. Previous training programs were adapted to restrictions of patients and targeted to facilitate exercise participation (e.g. home-based exercise or supported exercise at a clinic to assure comfortable training sessions for the patients), but were not individualized to enhance training adaptation. Moreover, the effect of disease severity and stage of disease on adaptation to training remains scarce. Fifth, most studies documented the intake of medication. Since it is well known that several active pharmaceutical ingredients interact with training adaptation processes, study outcomes might have been altered by drug intake. However, current data are insufficient to draw conclusions about these influences.

Conclusions

Based on the six included studies in this review, exercise training seems to be a safe and feasible treatment approach in HD patients. These studies on exercise training interventions in HD patients point to a beneficial effect of training on cardiovascular and mitochondrial function. Training effects on cognition, motor function, and body composition are less congruent, but overall evidence seems to support a possible positive effect. However, our conclusions are based on small-scale studies and cannot be transferred to all HD patients. To shed

more light on the effects of exercise training on the aforementioned variables, longer-term intervention studies with larger HD cohorts are desirable. For reasons of safety, it is recommended that all exercise training interventions are accompanied by frequent assessments to detect any accelerated worsening of symptoms.

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